MEDICAL GRAND ROUNDS

Chronic Obstructive Pulmonary Disease

January 12, 1967

I. Definition
   A. Asthma
   B. Bronchitis
   C. Emphysema

II. Etiology and Pathogenesis
   A. Physical or chemical irritation
      1. Inhalation of tobacco smoke
      2. Air pollution local or general
         a. Molds and other organic particulate matter
         b. Gases and vapors
         c. Inorganic particulate matter
      3. Aspiration - gastroesophageal reflux
   B. Infection
      1. Viral
      2. Bacterial
   C. Occlusive vascular disease
   D. Climatic factors
   E. Host factors
      1. Allergy
      2. Genetic disorders
         a. Cystic fibrosis
         b. Marfan's
         c. Gamma globulin deficiency
         d. Alpha-1-antitrypsin deficiency

III. Pathological Characteristics
   A. Asthma
      1. Bronchospasm
      2. Edema
      3. Bronchial hypersecretion
      4. Cellular infiltration
      5. Desquamation
   B. Bronchitis
      1. Bronchorrhea
      2. Mucous gland hyperplasia
      3. Desquamation
      4. Metaplasia
      5. Necrosis
   C. Emphysema
      1. Panlobular
         a. Alveolar wall fenestration and separation
         b. Capillary thrombosis and obliteration
         c. Confluence of spaces

2. Centrilobular
   a. Bronchiolitis
   b. Necrosis
   c. Dilitation of respiratory bronchioles
   d. Disruption of alveolar walls
3. Other types

IV. Radiological Characteristics - Bronchitis and Emphysema
A. Only advanced disease is diagnosable on routine X ray
   1. Overdistension
   2. Cystic space formation
   3. Flattened diaphragm, diminished motion and thinning of cardiac silhouette
   4. Increased anterior clear space
   5. Diminished vascular marking especially mid and peripheral lung fields
   6. Enlargement of hilar vessels and RH enlargement
B. Bronchogram
   1. Cystic bronchial wall change
   2. Distortion of bronchi
   3. Dilitation of peripheral air spaces
C. Angiogram
   1. Absence of capillaries
   2. Formation of cystic avascular spaces
   3. Abrupt tapering of big vessels

V. Physiological Disturbances
A. Ventilatory defect - obstructive
B. Increase in functional residual capacity, residual volume and total lung capacity
C. Uneven distribution ventilation/blood flow relationships - gas exchange abnormalities
   1. Hypoxia - early - improves with exercise
      - late - worsens with exercise
   2. Hypercapnia - respiratory acidosis decompensated - compensated
D. Metabolic disturbances
   1. Lactic acidosis
   2. Hypochloremic alkalosis
E. Diminished CO transfer coefficient (D_L) in relation to destructive lung disease

VI. Treatment
A. Acute failure
B. Chronic care
C. Rehabilitation

Case Histories

1. [redacted]. - A 54 year old [redacted], his chief complaint was progressive exertional dyspnea and who has smoked one to two packages of cigarettes a day for 35 years. He gave no history of cough or frequent respiratory infections prior to [redacted] of 1966, when he developed a severe respiratory infection accompanied by cough and sputum production which persisted with some improvement after he quit smoking in [redacted] of 1966. He had a 35 pound weight loss in the last six months. There was no history of allergy and no members of the family were known to have lung disease. The physical examination revealed evidence of recent weight loss. There was a mild increase in AP diameter of the chest. Chest wall motion was somewhat limited. The lungs were markedly hyperresonant to percussion. Breath sounds were diminished and there was a sustained wheeze on forced expiration. There was no clubbing or cyanosis. Laboratory studies revealed a hemoglobin of 16.5 gm with a hematocrit of 50%. Sputum smears revealed a great deal of acute and chronic inflammatory debris with some cellular atypism and evidence of squamous metaplasia. Chest X rays revealed some evidence of slight overdistension and some increase in lung markings. ECG revealed evidence of pulmonary hypertension with clockwise rotation, "P pulmonale" in leads II, III and AVF and low voltage. After a period of treatment the electrocardiogram was within normal limits. Pulmonary function studies are shown in Table 1. Pulmonary angiogram done by pulmonary artery injection revealed rapid lung transit with a profound diminution in the pulmonary capillary bed, the most normal area being the upper lobes. Pulmonary artery mean pressure was about 20 mm Hg.

Treatment consisted of intensive bronchial hygiene with nebulization procedures including bronchodilator agents; steroids, breathing training and physical rehabilitation. The patient showed a marked symptomatic improvement with only minimal change in ventilatory function and he was discharged to continue on this program with the hope of ultimate withdrawal of steroid therapy.

This is an example of moderate to moderately severe diffuse emphysema probably predominantly of the panlobular type and with an indeterminant but probably small degree of bronchiolitis. The long range response to therapy will do much to clarify the degree to which the functional derangement is due to peripheral airway obstruction of a reversible type.

2. [redacted]. - A 47 year old [redacted] worker who has smoked one or more packages of cigarettes per day for about 30 years. He quit one year ago. He has had marked nasal congestion, postnasal drip, cough and frequent upper respiratory infections for ten to fifteen years, with increasing in frequency and severity. Two years ago exertional dyspnea with wheezing appeared and became

progressively worse. Past medical history and family history were not particularly pertinent. The physical examination revealed a moderately obese slightly plethoric individual. The AP diameter of the chest is increased but there is no fixation of the thoracic cage and diaphragmatic motion was good. Expiration was slowed and there was a mid-expiration wheeze with scattered inspiratory coarse rales and rhonchi as well as scattered areas of diminished breath sounds. Chest X ray revealed some evidence of increased transradiancy and there was some increase in major bronchovascular markings. The pulmonary angiogram reveals evidence of diffuse central lobular emphysema with scattered areas of normal appearing lung pattern. The electrocardiogram showed evidence of pulmonary hypertension with clockwise rotation P pulmonale in II, III and AVF and diminished voltage. After a period of treatment the electrocardiogram was within normal limits.

The treatment consisted of intensive nebulization therapy with a transient increase in steroid therapy, weight reduction, breathing training and increased physical activity. This resulted in a marked symptomatic and functional improvement with large volumes of sputum production. Pulmonary function studies are listed in Table 2.

This is an example of severe chronic bronchitis with central lobular emphysema. In spite of the clear-cut evidence of a considerable amount of degenerative lung disease this patient has the potential for a considerable amount of both symptomatic and functional improvement. The immediate objective will be to completely eradicate the patient's bronchitic symptoms by continuing the present treatment program including steroids; when achieved a gradual reduction to maintenance treatment will be attempted with no intention necessarily of ever discontinuing treatment entirely.

3. [redacted]. - A 59 year old man is a [redacted] working largely with wheat and other grains. He was first seen in [redacted] of 1963 at the age of 59. He had smoked one to two packs of cigarettes per day for 35 years, and in addition for periods of eight to ten weeks once or twice each year he was exposed to heavy concentrations of grain dust and actually smoked during these periods. He had symptoms of mild asthmatic bronchitis for over fifteen years and was first aware of exertional dyspnea while hunting at high altitude in 1950. In 1959, he began to have frequent respiratory infections with cough, mucopurulent sputum, and increased dyspnea. In 1962, when hospitalized for a hernia repair at [redacted] he was told he had pulmonary emphysema and although he was advised to quit smoking he continued to smoke until 1963 when he was first seen. The only other thing in his history of note was the fact that for many years he has had difficulty sleeping on his left side because of nocturnal respiratory distress.

Physical examination revealed normal vital signs and otherwise revealed evidence of classic manifestations of chronic obstructive pulmonary disease with bullous change in the right lung. There was general overdistension of the chest especially on the right with diffuse inspiratory and expiratory wheezing with crackling rales and rhonchi. His cough was productive of moderate amounts of mucopurulent sputum. Breath sounds were good in the left chest but moderately diminished on the right. There is generalized increase in transradiancy of the right chest especially in the left upper lateral chest where a bullous lesion 15 by 7 cm was seen. There is also evidence of bullous change in the right lower chest. Bronchovascular markings show minimal displacement.

An intensive program of bronchial hygiene consisting of four or more periods of treatment each day with nebulized bronchodilator followed by a 45 minute period of inhalation of a warm mist saline propylene glycol solution was instituted and the patient was advised to abstain totally from smoking which he did. Except for one or two mild short term upper respiratory infections the patient did very well, was completely free of cough and sputum production except during respiratory infections. Late in 1965, he had a severe upper respiratory infection and his exertional dyspnea increased at that time and slowly worsened up until he was seen in August of 1966, at which time there was clear-cut evidence of marked enlargement of the bullous area in the right lung and there was major functional deterioration. The pulmonary angiogram revealed an air containing space occupying virtually the entire right chest with compression of the vasculature to the right upper and right lower lung areas compressed into the mediastinum. Although the left lung revealed some evidence of degenerative change the vasculature looked quite good considering the magnitude of this patient's problem. On this basis plus the hope that the functioning lung could be recovered on the right surgery was undertaken to remove the bullous lesion.

The postoperative period was quite stormy. The patient had a major air leak, a severe staphylococcal empyema which fortunately was due to a very sensitive organism. The patient improved steadily and rapidly after the 10th day, postoperatively. He is now both symptomatically and functionally better than he has been in ten years or more. Postoperative diffusion studies have not yet been performed because the patient was still rapidly improving when last seen in October.

4. [redacted] - A 53 year old [redacted] currently [redacted] therapist who gave a history of having had a considerable amount of gastrointestinal difficulty since 1929 when he was found to have a peptic ulcer. In the late 1940's he started having occasional episodes of nocturnal coughing which he associated with eating heavy meals late in the evening because he often recognized bits of food in the material he coughed up. He also started having some difficulty

with recurrent sinus infections for which a tonsillectomy and two radical antrum operations were performed in 1958. At the same time he noted that he got coughing colds with sputum production more frequently than he used to in the past. He was found to have a hiatus hernia which was treated surgically through a thoracic approach. He got along extremely well for several years until 1962, when he again began to have coughing and choking spasms especially when he was under considerable emotional tension and at nights. In 1964, he began to have a fairly frequent attacks of asthma. A repeat X ray of the upper GI tract in 1965, revealed a small hiatus hernia. When he had two extremely severe nocturnal attacks of asthma where he was discovered by his wife to be unresponsive and suffocating, both episodes necessitating hospitalization for acute respiratory failure, he was referred for evaluation of his respiratory problems. Physical examination revealed a vigorous healthy 53 year old man whose only abnormal physical findings were confined to the chest where diffuse musical rales and coarse rhonchi were heard throughout the chest on both inspiration and expiration. Marked clearing occurred following the administration of a bronchodilator agent with the expectoration of some mucoid secretions. Sputum smears revealed 90% eosinophils in the sputum and a CBC which was otherwise normal revealed 8% eosinophils. Culture revealed a moderate growth of Klebsiella. EKG was normal. Chest X ray revealed no abnormalities except for a slight overdistension and some increase in bronchovascular markings. Pulmonary function studies are shown on Table 4. His maximal oxygen intake was normal at 2.6 L/min and a heart rate of 174/min. Repeat cineflourographic examination of the upper CI tract revealed a large hiatus hernia with "wide open gastroesophageal reflux." Postprandial gastric secretions revealed a moderate to marked increase in hydrogen ion concentration.

This is a clear-cut example of asthmatic bronchitis largely due to recurrent aspirations from gastroesophageal reflux. Since the previous repair had failed conservative management was recommended.

He has gotten along quite well on a program of intensive bronchial hygiene with bronchodilator and saline mist inhalation three to four times daily, intensive antacid therapy, and sleeping in a head-up position with the head end of his bed elevated some 30^{o}. He has had one attack since that time precipitated by his own carelessness which he readily acknowledges. He recognizes that he must avoid eating rapidly, must avoid eating heavy meals especially in the afternoon or evening, must never neglect his antacid treatment and must avoid adopting positions which tend to enhance reflux.

5. [redacted] - A 39 year old [redacted] who had been a heavy cigarette smoker for 17 years. For ten years prior to examination he had had recurrent episodes of upper respiratory tract infection with rhinitis and sinusitis predominantly but subsequently

with cough and sputum production. He has also had a history of nasal polyps which responded to steroid therapy but repeated allergy investigations failed to yield anything but a skin test sensitivity to house dust. He always exhibited moderate to marked eosinophilia in the peripheral blood and invariably more than 90% eosinophils in nasal and bronchial secretions. His problem had never followed a seasonal pattern except that it was worse during the fall and winter months in association with respiratory infections. When first seen in 1961, he was hospitalized for a protracted episode of suppurative bronchitis and progressive weight loss and respiratory insufficiency. After a protracted and stormy course he finally responded to intensive bronchial hygiene therapy with high dose steroids and high dose bronchodilator therapy including both aerosol bronchodilator and virtually continuous aminophylline either intravenously or rectally. Clearing and improvement was accompanied by the evacuation of large volumes of thick mucopurulent material with solid bronchial plugs. His function studies are shown in Table 5. It was necessary to continue an intensive program of therapy along the lines mentioned above and steroid which was started at a level of 60 mgm per day of Prednisone, continued at levels of 40 mgm per day for nearly six months. Prednisone was gradually reduced to 20 mgm per day and continued at this level for two years. In late 1964, it was possible to reduce steroid dosage to 10 mgm per day, and subsequently his dose has varied in accordance with his symptoms from 10 mgm every other day to 10 mgm a day. Initially his sputum was heavily infected with Pseudomonas which cleared with clearing of his airways and improvement of his ventilatory function. All antibiotics were discontinued at the time the program of intensive bronchial hygiene was started. The patient has had no major difficulty since that time and has not missed more than one or two days of work in the last five years.

This is a classic example of asthmatic bronchitis in a patient who shows evidence of hypersensitivity but in whom no specific etiology can be ascertained. The possibility of fungus or mite hypersensitivity has not been excluded. There is no significant evidence of degenerative lung disease, but surely there is evidence of persistent degree of bronchiolitis which is largely reversible to aerosol bronchodilator.

6. [redacted] - A 39 year old [redacted] driver has been a moderate to heavy cigarette smoker since the age of 15. He denies symptoms prior to 1961, at age 33, when he first noted exertional dyspnea and intermittent evidence of chronic bronchitis. He was told at that time that he had radiological evidence of pulmonary emphysema. Since that time he has had a fairly rapid course of developing respiratory insufficiency with evidence of degenerative lung disease. Pulmonary function studies are shown in Table 6. This patient was found to have homozygotic type deficiency in alpha-1-antitrypsin, i.e., his level was less than 10% of normal. A family study has been done on this and two other patients by Dr. M. Tarkoff. Twenty-three blood relatives of this patient were available for examination,

and data is available on ten of these at this time, six of whom revealed a definite heterozygotic type deficiency in alph-1-anti-trypsin.

Fifteen patients with clinical and functional evidence of degenerative lung disease occurring under the age of forty have been examined, and three of these patients have revealed the defect.

TABLE 1

[redacted]	Pred.	BBD	ABD
FVC L	4.66	4.16	4.65
$FEV_{0.5}$	>60%	1.29 (31%)	1.56 (34%)
$FEV_{1.0}$	>75%	1.80 (43%)	2.23 (48%)
FEF_{0-25}	7.92	3.08	3.93
FEF_{25-75}	4.33	0.51	0.70
FIF	6.06	3.37	4.13

	Pred.	Obs.		Pred.	Obs.
TLC	6898	8438	T_LCO	31	20
FRC	3449	5793	D_M	83	37
RV/TLC	.31	.51	V_c	78	51
7min N_2%	<1.5	2.8			

TABLE 2

[redacted].	Pred.	8-15	9-23
FVC	4.71	3.14	5.46
$FEV_{0.5}$	>60% FVC	855 (27%)	2.57 (47%)
$FEV_{1.0}$	>75% FVC	1.19 (38%)	3.54 (65%)
FEF_{0-25}	8.01	1.41	5.67
FEF_{25-75}	4.38	0.37	1.87
FIF	6.12	4.97	8.55
TLC	6.19	--	8.10
FRC	3.10	--	4.28
RV/TLC	.23	--	.37
7min N_2%	<1.5	--	0.5
D_LCO	24	--	15
D_M	74	--	46
V_c	58	--	35

TABLE 3

[redacted], 59 yrs.	1963	1964	1965	1966 Pre	1966 Post	Pred.
FVC ml	2387	4144	3400	2790	3549	4110
$FEV_{0.5}$	590	753	760	606	1331	2670
$FEV_{1.0}$	800	1210	1080	923	1841	3300
FEF_{0-25} L/sec	1.18	1.40	1.36	1.07	3.42	6.98
FEF_{25-75}	0.20	0.41	0.36	0.28	0.69	3.82
FIF	3.78	5.64	5.99	5.35	5.15	5.35
VCET sec	20	18	13	8	2.5	<4
TLC ml	7495	--	--	5303		
FRC	4900	--	--	3466		
RV/TLC	.66	--	--	.49		
7min N_2%	6.2	--	--	4.0		
$PaCO_2$	42	39	--	56	32	
PaO_2	71	82	--	60	84	
pH	7.41	7.43	--	7.37	7.46	

	Forced	Slow		Obs.	Pred.
FVC	3.9	4.7	T_LCO	10 (37%)	27
$FEV_{1.0}$	1.1	1.4	D_M	27 (37%)	73
FEF_{0-25}	1.3	1.6	V_c	26 (35%)	74
FEF_{25-75}	0.3	0.3			

TABLE 4

[redacted]	Pred.	BBD	ABD
FVC ml	4860	4392 (90%)	4676 (96%)
$FEV_{0.5}$	>60%	2063 (47%)	2458 (53%)
$FEV_{1.0}$	>75%	2697 (61%)	3194 (68%)
FEF_{0-25} L/sec	8.26	6.77 (82%)	8.34 (101%)
FEF_{25-75}	4.52	1.03 (23%)	1.89 (42%)
FIF	6.32	6.13 (97%)	6.44 (102%)
VCET sec	<4.0	5.5	4.3

TABLE 5

	[redacted] 1961		[redacted] 1963		[redacted] 1964	
	Pred.	ABD	BBD	ABD	BBD	ABD
FVC	4.85	3.87	5.3	5.3	5.0	5.2
$FEV_{0.5}$	>60%	1.01 (28%)	2.7 (51%)	2.8 (52%)	2.9 (58%)	3.2 (62%)
$FEV_{1.0}$	>75%	1.48 (38%)	3.8 (72%)	3.9 (74%)	3.8 (76%)	4.1 (79%)
$FEF_{0-25\%}$	8.3	1.7 (20%)	5.9 (72%)	6.6 (80%)	9.7 (115%)	10.5 (128%)
$FEF_{25-75\%}$	4.5	0.4 (9%)	2.7 (59%)	2.9 (65%)	2.8 (60%)	3.8 (85%)
FIF	6.3	4.2 (67%)	5.3 (84%)	5.6 (89%)	6.0 (96%)	6.7 (106%)
TLC	<6.5	7.2 (110%)	---	7.25		
RV/TLC	<25%	46%	---	27%		
7min N_2 index	1.5%	3.2%	---	1.5%		

[redacted] 1961

	Room Air	100% O_2
SaO_2%	96	100
PaO_2 mm Hg	85	633
pH	7.45	7.45
$PaCO_2$ mm Hg	37	37
A-a O_2 grad.	25	30
$\dot{V}_{O_2}$	262	
$\dot{V}_{CO_2}$	200	
$PaCO_2$ end tidal	39 mm	
$PaCO_2$ end exp.	40 mm	
$PaCO_2$	38 mm	

[redacted] 1964

D_LCO	31 (110%)
D_M	84 (110%)
V_c	79 (112%)
TLC	7.29 (119%)
FRC	3.93 (127%)
RV/TLC	.35 (150%)
7min N_2%	0.7

TABLE 6

Vent. Func.	Pred.	Obs.
FVC L	4.550	3.071 (68%)
$FEV_{0.5}$	>60%	0.483 (16% of FVC)
$FEV_{1.0}$	>75%	0.702 (23% of FVC)
$FEF_{0-25\%}$ L/sec	7.74	0.60 (8%)
$FEF_{25-75\%}$	4.23	0.13 (3%)
FIF	5.92	4.80 (81%)

Lung Vol.	Pred.	Obs.	%
TLC ml	5910	10,437	177%
FRC	2955	8,895	301%
RV/TLC %	23%	72%	
7min N_2%	1.5%	11%	

Blood Gases	Rest	3 MPH Treadmill Exercise
pH	7.40	7.30
$PaCO_2$ mm Hg	47	49
PaO_2	55	49
O_2 sat.%	87	79
Min. Vol.L/min	5.9	16.4
O_2 consump. ml	112	513

Diffusion	Pred.	Obs.	%
D_LCO cc/min/mm Hg	19	6	32%
D_M cc/min/mm Hg	70	16	23%
V_c ml	42	17	40%

REFERENCES

REVIEWS AND MONOGRAPHS

1. Orie, N. G. M., and Fluter, H. J.: Bronchitis, I. First International Symposium, Univer. of Groenigan, the Netherlands, Charles C. Thomas, Publisher, 1961.

2. Ibid., Bronchitis, II. Second International Symposium, Univer. of Groenigan, the Netherlands, Charles C. Thomas, Publisher, 1964.

These two books are the proceedings of two conferences on the subject of bronchitis. The participants in the conference were 45 of the world's outstanding authorities on the subject from England and Europe. Each session in the first conference dealt on a different aspect of the subject ranging all the way from definitions through therapy. The second conference dealt with two broad general aspects of the problem: 1. factors in etiology and pathogensis and 2. treatment.

3. Mitchell, R. A.: Cerebrospinal fluid and the regulation of respiration. In: Advances in Respiratory Physiology, edited by Collin G. Caro, Williams and Wilkins, Co. Baltimore, 1966.

This review emphasizes the important role of two groups of chemoreceptors in regulation of respiration: 1. The carotid and aortic bodies which sense changes in arterial O_2 tension, hydrogen ion concentration, and CO_2 tension, and 2. the medullary hydrogen ion receptors on the ventral lateral surface of the medulla which sense changes in CSF hydrogen ion concentration. This review with it's 151 references along with the reviews of Posner and Plum, No. 39 and Bleich, et al No. 42 bring the current knowledge of the relationships between CSF and arterial blood gas functions clearly into focus.

4. Widdicombe, John G.: Regulation of bronchial calibre. In: Advances in Respiratory Physiology, edited by Collin G. Caro, Williams and Wilkins Co. Baltimore, 1966.

This review considers the mechanical, nervous, and chemical forces that act in the tracheobronchial tree and how the interreaction of these influences may be exhibited in a number of physiological conditions. This very provocative review with over 100 references will be of interest to those having more than a passing interest in factors concerned in the control of airway caliber.

5. Seventh Annual Conference on Research in Emphysema, Aspen, Colo. June 1964. Pathogenesis of the chronic obstructive bronchopulmonary disease. Edited by Mitchell, R. S. and Herzog, H., S. Karger Co. Basel, Switzerland and New York, 1965.

The topics discussed include clinical and environmental studies, alveolar surfactant, pulmonary circulation, lung morphology, structural and functional differences and relationships between emphysema and bronchitis, and miscellaneous topics such as mucociliary insufficiency and the role of various inhalant agents.

6. Symposium on Structure, Function and Measurement of Respiratory Cilia. Duke Univ. Med. Center, Feb. 1965. Amer. Rev. Resp. Dis. 93: supplement. March 1966.

The following general topics were discussed: 1. the ciliated cell, 2. measurement of ciliary action, 3. responses of ciliated epithelium to irritants, 4. effects of bacteria and virus on ciliated epithelium. There were 53 participants from all parts of the country, and 17 papers were presented at the two day conference. Ciliary function in the intact human being is obviously a complex business which is very difficult to study: most of what is presented are animal studies. Many agents are ciliostatic including cigarette smoke, cold, drying of the mucous membrane and even mucomyst and alcohol. Most agents that produce objective irritation do exhibit ciliostatic effects. Things which seriously alter cell metabolism also cause ciliostasis such as hypoxia and hypercapnia as well as metabolic disturbances. Aminophylline, isuprel and digitalis are among those things known to be ciliary stimulants.

PATHOGENESIS

7. Mitchell, R. F., Ryan, S. F., Petty, T. L., and Filly, G. F.: The significance of morphologic chronic hyperplastic bronchitis. Amer. Rev. Resp. Dis. 93:720, 1966.

This study clearly emphasizes the complex nature of the group of overlapping disorders covered by the designation of chronic, obstructive pulmonary disease.

8. Gross, P., Pfitzer, E. A., and Hatch, T. F.: Alveolar clearance: Its relation to leisions of the respiratory bronchiole. Amer. Rev. Resp. Dis. 94:10, 1966.

9. Gross, P., Babyak, M. A., Tolker, E., and Kaschak, M.: Enzymatically produced pulmonary emphysema. J. Occupational Med. 6:481, 1964.

These studies call attention to the vulnerability of the bronchoalveolar segment of the lung and the likely relationship of exposure to irritant substances when accompanied by ciliary stasis in the pathogenesis of degenerative lung disease.

10. Green, G., and Kass, E. H.: Factors influencing the clearance of bacteria by the lungs. J. Clin. Invest. 43:769, 1964.

Alcohol, hypoxia, starvation and to a mild degree, steriods impair pulmonary clearance.

11. Ham, J. C.: Acute infectious obstructing bronchiolitis: potential fatal disease in the adult. Annals of Int. Med. 60:47, 1964.

12. Davies, G. M.: Fog bronchiolitis. Lancet 1:580, March 1963.

These two papers which report 19 cases in considerable detail are the first reports since the classic studies of McLean, Australian Annals of Int. Med. 5:254, 1956 and 6:29, 1957. Except in those situations where anatomical material is available, the differentiation of bronchiolitis from alveolitis clinically is probably very difficult if not impossible.

13. Foley, D. F., and Lowe, F. C.: Equine centrilobular emphysema with further observations on pathology of heaves. Amer. Rev. Resp. Dis. 93:17, 1966.

14. McLaughlin, R. F., Jr., and Edwards, D. W.: Naturally occurring emphysema, the fine gross and histopathologic counterpart of human emphysema. Amer. Rev. Resp. Dis. 93:22, 1966.

In earlier studies McLaughlin showed the similarity between the subgross anatomy of the equine lung and the human lung, and these studies report the identical lesions of bronchiolitis and emphysema in the horse as seen in man.

15. Anderson, A. E., Jr., Hernandez, J. A., Eckert, P., and Forakera, G.: Emphysema in lung macrosections correlated with smoking habits. Science 144:1025, 1964.

16. Mitchell, R. S., Vincent, T. N. and Filly, G. F.: Cigarette smoking in chronic bronchitis and emphysema. JAMA 188:132, 1964.

17. Auerbach, O., et al: Experimental production of pulmonary emphysema in smoking dogs. To be published.

These studies and many others continue to add impact to the evidence already available to indict cigarette smoking as the single most significant etiologic factor in the development of pulmonary emphysema.

18. Kobayashi, M., Stahmann, Mark A., Rankin, J., and Dickie, H. A.: Antigens in moldy hay as a cause of farmer's lung. Proceedings Soc. Exp. Biolo. in Med. 113:472, 1963.

19. Williams, J. V.: Inhalation in skin tests with extracts of hay and fungi in patients with farmer's lung. Thorax 18:182, 1963.

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21. Moskowitz, R. L, Lyons, H. A., and Cottle, H. R.: Silo filler's disease: clinical, physiologic and pathologic study of a patient. Amer. J. Med. 36:457, 1964.

These are just a few of a large number of papers which have been published in the last two or three years describing a variety of agents known to produce chronic obstructive pulmonary disease as a result of inhalation of these chemotoxic or antigenetically active substances. The large number of potentially dangerous substances in man's atmosphere should alert all to the possible etiologic relationship of such agents to chronic respiratory symptoms.

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Another possible related etiologic factor genetically determined has been described. The incidence of the defect in patients with chronic obstructive pulmonary disease is apparently rare. However, our own studies on patients under forty years of age with clinical evidence of degenerative lung disease reveal a much higher incidence. Three out of 15 have shown the defect.

26. Burrell, R. G., Esber, H. J., Hagadorn, J. E. and Andrews, C. E.: Specificity of lung-reactive antibodies in human serum. Amer. Rev. of Resp. Dis. 94:743, 1966.

27. Hagadorn, J. E., Burrell, R. G., and Andrews, C. E.: Immunochemical analysis of lung-reactive antibodies in human serum. Amer. Rev. of Resp. Dis. 94:751, 1966

The specificity and significance of lung-reactive antibodies remains unclear.

28. Ryan, S. F.: Pulmonary embolism and thrombosis in chronic obstructive emphysema. Amer. J. Path. 43:767, 1963.

In 66 cases with progressive disabling dyspnea for at least 6 months prior to death, the cause of death in every instance was considered to be pulmonary emphysema uncomplicated by valvular or congenital heart disease. Pulmonary embolization was found in 44% of the cases. Polycythemia was found in 43% of the cases, some with emboli and some without. Ninety percent of the emboli were large. In a matched controlled series the incidence of pulmonary embolism was only 15%, and only 70% of these were large. Of significance is the fact that pulmonary embolism occurs with severe chronic obstructive pulmonary disease as frequently as it does in heart failure even though neither polycythemia nor heart failure may be present in the patients with pulmonary disease.

29. Glauser, E. M.: Experimental production of acute pulmonary emphysema in newborn piglets. Amer. Rev. Resp. Dis. 94:873, 1966.

This very interesting study in which severe hyperventilatory stress was imposed by 10% CO_2 and 7% oxygen breathing for 24 hours on newborn piglets produced marked weight loss in the animals without increased urine excretion, marked acidosis, hypoxia and hypercapnia with anatomical changes characteristic of acute disruptive disease of the lung parenchyma.

PATHOLOGICAL

30. Kory, R. C., Rauterkus, T. L., Korthy, A. L., and Côté, R. A.:

Quantitative estimation of pulmonary emphysema in lung macrosections by photoelectric measurement of transmitted life. Amer. Rev. Resp. Dis. 93:758, 1966.

A fairly simple and reasonably precise method for estimating the degree of lung destruction which will no doubt be useful in correlating clinical and physiological changes with structural abnormalities.

PATHOLOGICAL - ROENTGENOLOGICAL

31. Simon, George: Radiology and emphysema. Clin. Rad. 15:293, 1964.

If the central dome of the right diaphragm is at or below the seventh rib anteriorly, the diaphragm is flattened. The sixth rib is acceptable in a hypersthenic patient. Diaphragm excursion is less than 3 cm. Normally, should be more than 4 cm. The retrosternal space which is normally a maximum of 2-3 cm. is more than 3 cm. The clear space extends lower in emphysema; normally it rarely gets as close as 3 cm to the diaphragm. The narrow verticle heart and enlarged pulmonary artery are also characteristic. (These changes are those of advanced emphysema; when they are present, invariably clinical signs and symptoms as well as functional abnormalities are present.) Heart failure and obesity may obscure these findings.

32. Reid, Lynne, and Millard, F. J. C.: Correlation between radiological diagnosis and structural lung changes in emphysema. Clin. Rad. 15:307, 1964.

Grade III out of IV emphysematous change, i.e. air spaces 5 mm. or more must be present to permit radiological diagnosis.

Emphysema in upper lobes does not effect diaphragm except in advanced bullous disease. Lower lobe emphysema nearly always depresses the diaphragm.

33. Nicklaus, T. M., Stowell, D. W., Christiansen, W. R., and Renzetti, A. D., Jr.: The accuracy of the roentgenologic diagnosis of chronic, pulmonary emphysema. Amer. Rev. Resp. Dis. 93:889, 1966.

This study revealed that interpretations of experienced readers of chest X-rays accurately diagnose moderate to severe degrees of pulmonary emphysema with only rare false diagnoses.

34. Jefferson, K. E., Reid, Lynne, Skerrow, G. D., and Simon, George: The normal pulmonary angiogram and some changes seen in chronic nonspecific lung disease. Proc. Royal Soc. Med. 58:677, Sept. 1965.

A collected summary of published material on pulmonary angiography in patients with chronic, obstructive pulmonary disease, a clinical and physiological correlation.

35. Takino, M., and Takino, Y.: Surgical removal of the carotid body and its relation to the carotid chemoreceptor and baroreceptor reflex in asthmatics. Dis. Chest 47:129, 1965.

"Since Seo and Nakayama 1942 and Nakayama 1961 reported the effective glomectomy in bronchial asthma, the operation seems to be gaining popularity in foreign countries. However, this treatment went out of fashion in Japan ten years ago, because of its nearly temporary effect, despite its dramatic effect in some cases."

This is a study of 102 patients having either unilateral or bilateral glomectomy. More than 40% showed no improvement at all. Eighty % of those showing some improvement relapsed within a year. Eighty-three of the 102 cases were operated in the first five years of this study. Only five patients have been operated in the last five years.

PHYSIOLOGICAL

36. Renzetti, A. D., Jr., McClement, J. H., and Litt, D.: Mortality in relation to respiratory function in chronic obstructive pulmonary disease. Amer. J. Med. 41:115, 1966.

These authors report a correlation between initial pulmonary function studies and mortality over a four year period of follow-up; a history of an episode of right heart failure was found to be the most significant single factor relating to mortality. Of special significance was the higher incidence of cor pulmonale and the earlier mortality in relation to other functional alteration in people living at high altitudes. In this series 96.4% of the patients with COPD were cigarette smokers.

37. Sukumalchantra, Y., Dinakara, P., and Williams, M. H., Jr.: Amer. Rev. Resp. Dis. 93:215, 1966. Prognosis of patients with chronic obstructive pulmonary disease after hospitalization for acute ventilatory failure: A three year follow-up study.

This is a controlled study on patients with chronic, obstructive pulmonary disease. A group having been in acute ventilatory failure on one or more occasions was compared with a group not previously in respiratory failure. Although there is some evidence that relatively normal steady state diffusing capacity and arterial blood gas content are associated with a favorable prognosis in patients with chronic obstructive pulmonary disease, death in this condition is largely due to acute ventilatory failure that cannot be anticipated accurately from the knowledge of pulmonary function alone.

38. Bentivoglio, L. G., Beerel, F., Stewart, P. B., Bryan, A. C., Ball, W. C., Jr., and Bates, D. V.: Studies of regional ventilation and perfusion in pulmonary emphysema using xenon 133. Amer. Rev. Resp. Dis. 88:315, 1963.

This is a very exciting but extremely complicated and expensive method for studying ventilation and perfusion relationships in the lung. By scanning with scintillation counters over various regions of the lung, perfusion can be evaluated by the injection of radioactive xenon in saline which will then be found to appear in proportion to the perfusion of the particular regions of the lung. Breathing a gas mixture containing radioactive xenon will reveal the degree to which various areas of the lung are well ventilated. Ventilation is 2 - 4 times

greater than perfusion in all areas of the lung in patients with emphysema. In a normal individual, ventilation exceeds perfusion slightly in the upper zones of the lung. They tend to be equal in the mid-zones, and in the lower zone perfusion tends to exceed ventilation by a modest degree.

39. Posner, J. B., Swanson, A. G. and Plum, F.: Acid base balance in cerebral spinal fluid. Arch. Neurol. 12:479, 1965.

These studies demonstrate that the PCO_2 of the CSF is approximately 10 mm higher than blood PCO_2 and bicarbonate 0.5 mEq. lower. Hydrogen ion concentration is thus slightly higher in CSF. The PCO_2 parallels that of the arterial blood in all conditions, but the difference increases in metabolic alkalosis causing the CSF acidosis to persist. This emphasizes a necessity for avoiding respiratory alkalosis in the post-hypercapneic states. Likewise, excessive rapidity in reduction of arterial PCO_2 leads to exaggerated metabolic alkalosis in the CSF. In either event marked disturbances in cerebral function may eventuate. This suggest the importance of examination of the CSF, acid base balance when CNS disturbances persist.

40. Bleich, H. L., Tannen, Richard L., and Schwartz, William B.: The induction of metabolic alkalosis by the correction of potassium deficiency. J. Clin. Invest. 45:573, 1966.

Potassium deficient dogs without metabolic alkalosis when fed potassium sulfate or neutralphosphate retained potassium, and rather than excrete sodium excreted nearly an equivalent quantity of hydrogen and developed metabolic alkalosis. Normal dogs on a chloride free diet treated in the same fashion do not develop metabolic alkalosis.

41. Cohen, J. J., and Schwartz, W. B: Evaluation of acid-base equilibrium in pulmonary insufficiency. (Editorial) Amer. J. Med. 41:163, 1966.

Sixteen most pertinent references. Knowledge of the nature of the acid-base disturbances associated with CO_2 retention is of both diagnostic and therapeutic significance. The authors summarize their work on metabolic studies during acute and chronic CO_2 retention both in dogs and man. The nature of the two kinds of response to CO_2 retention, the immediate tissue, and blood buffering and the more delayed renal response to acidosis with increased HCO_3 reabsorption are discussed.

From this group's studies a very useful graph, Figure 2, has been drafted to help demonstrate the significance of changes in CO_2 tension with respect to H^+ concentration.

42. Bleich, H. L., Berkman, P. M., and Schwartz, W. B.: The response of cerebrospinal fluid composition to sustained hypercapnia. J. Clin. Invest. 43:11, 1964.

Dogs exposed to 12% CO_2 continuously showed a gradual rise of CSF HCO_3 to approximately 13 mEq. within the first 24 hours with no subsequent rise over a 24 hour period. The steady state in the plasma was not achieved so quickly. Chloride decreases in both compartments were nearly identical to the bicarbonate rise. There was no significant change in sodium or potassium.

43. Enson, Y., Guintini, C., Lewis, M. L., Morris, T. Q., Ferrer, M. I., and Harvey, R. M.: The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J. Clin. Invest. 43:1146,1964.

44. Rudolph, A. M., and Yuan, S.: Response of the pulmonary vasculature to hypoxia in hydrogen ion concentration changes. J. Clin. Invest. 45:399, 1966.

These two studies clearly indicate the interdependence of hypoxia and increased hydrogen ion concentration in producing profound increases in pulmonary vascular resistance and pulmonary artery pressure which is immediately reversible with correction of the acidosis.

45. Sackner, M. A., Feisal, K. A., and Karsch, D. N.: Size of gas exchange vessels in the lung. J. Clin. Invest. 43:1847, 1964.

More than ninty percent of gas exchange apparently at level 8-20 micron sized blood vessels.

TREATMENT

46. Davis, A. L., Grobow, E. J., Kaminski, T., Tompset, R., and McClemet, J. H.: Bacterial infection and some effects of chemoprophylaxis in chronic pulmonary emphysema: II. Chemoprophylaxis with daily chloramphenicol. Amer. Rev. Resp. Dis. 92:900, 1965.

The results of this and other studies lead the authors to conclude that chemoprophylaxis does not seem to be indicated for the majority of patients with chronic bronchitis and emphysema despite a possible beneficial effect of long term antimicrobial therapy and reducing the incidence or duration of acute exacerbations. It is not the principal mode of treatment of chronic respiratory disorders. Even though there are some who would argue with this point of view, it is probably the best reflection of current experience with a few exceptions, and certainly it must be emphasized that the best prophylaxis against bacterial exacerbations is the avoidance of other sources of bronchial irritation including viral infections and the maintenance of ideal bronchial hygiene. This study and the reviews by Mulder and Lynne Reid in Advances in Int. Med. 12: 1964, Yearbook Med. Pub., Inc. raise a serious question in the minds of many as to whether Hemophilus influenza which is frequently found in patients with chronic bronchitis during exacerbation is the cause of the exacerbation or the consequence of the exacerbation.

47. A statement of the committee on therapy of chronic, obstructive lung disease. Amer. Rev. Resp. Dis. 92:513, 1965.

Aside from a few unsupported or unexplained statements such as, "The use of nebulized forms of epinephrine should be restricted to three or four times in 24 hours," and, "Nebulized wetting agents may make breathing more difficult in severe respiratory insufficiency"; this is a very concise and complete statement.

48. Bates, J. H., Adamson, J. S., and Pierce, J. A.: Death after voluntary hyperventilation. New Eng. J. Med. 274:1371, 1966.

49. Addington, W. W., Kettel, L. J., and Cugell, D. W.: Alkalosis due to mechanical hyperventilation in patients with chronic hypercapnia. Amer. Rev. Resp. Dis. 93:736, 1966.

50. Feldman, R., and Williams, H. M., Jr.: Acute ventilatory failure. New York J. Med. 63:3355, 1963.

51. Lyons, H. A., Becker, W. H., and Torres, G. E.: Management of severe pulmonary emphysema. Amer. J. Med. 36:62, 1964.

52. Sukumalchantra, Y., and Williams, M. H., Jr.: Pathophysiology of ventilatory failure. Amer. Rev. Resp. Dis. 92:428, 1965.

53. Refsum, H. E.: Arterial hypoxemia and centrolobular liver cell necrosis in pulmonary insufficiency. Clin. Sci. 25:369, 1963, and Acta Med. Scand. 176:473, 1964.

54. Chamberlain, D. A., and Millard, F. J. C.: Treatment of polycythemia secondary to hypoxic lung disease by continuous oxygen administration. Quar. J. Med. 32:341, 1963.

55. Hutchinson, D. C. S., Flenley, D. C., and Donald, K. W.: Controlled oxygen therapy in respiratory failure. Brit. Med. J. 2:1159, 1964.

56. Campbell, E. J. M.: Oxygen therapy in diseases of the chest. Brit. J. Dis Chest 58:149, 1964.

57. McNicol, M. W., and Campbell, E. J. M.: Severity of respiratory failure arterial blood gasses in untreated patients. Lancet 1: 336, Feb. 13, 1965.

58. Lal, S.: Blood gases in respiratory failure: state on admission to hospital and management. Lancet 1:339, Feb. 13, 1965.

All these reports on severe respiratory insufficiency serve to emphasize several points. 1. Death is a result of hypoxia and hypercapnia and the consequences stemming therefrom. 2. Accurate serial monitoring of blood gases, pH and electrolytes as well as certain other vital functions is mandatory to successful treatment. 3. Whereas hypoxia must be corrected promptly and continuously, oxygen administration should always be carefully controlled. Seldom are concentrations of inspired oxygen in excess of 30-40% necessary to maintain acceptable levels of oxygen tension, i.e., better than 70 mm Hg. 4. Adequate ventilation must be provided to restore arterial CO_2 to reasonable levels, i.e., that which is compatible with the best unassisted ventilatory capacity of which the patient is capable. When hypercapnia is acute and severe respiratory acidosis is present, rapid correction of the hypercapneic state is in order. When hypercapnia is chronic and most of the retained CO_2 has been buffered as indicated by the near normal pH, the hypercapneic state should be corrected slowly using hydrogen ion con-

centration as the guide to the rate at which correction should be executed. 5. Patients with severe respiratory failure superimposed on chronic pulmonary disease, especially if they have chronic hypercapnia and have received steroids or diuretics and have been placed on salt restriction with free access to water, often have severe states of potassium and chloride depletion and occasionally sodium depletion, even though these may not be reflected by admission serum concentration values. The need for prompt replacement therapy with potassium chloride and sodium chloride must be anticipated. 6. Ultimate correction of the problems of respiratory failure pends on improvement of ventilatory function which must immediately be provided by establishment of an effective airway by aggressive tracheal suctioning with or without transtracheal vinyl catheter intubation to permit tracheal instillation of materials to promote bronchial evacuation or by endotracheal intubation of or by a tracheostomy as the circumstances may dictate. 7. Finally, it must be remembered that maintenance of gas exchange homeostasis is not the sole objective of mechanical ventilatory assistance. Clearing of inflammatory exudate and restoration of the mechanical integrity of the respiratory system is the ultimate and often overlooked aim of aggressive mechanical measures which include vigorous chest percussion and postural drainage.

59. Addis, G. J.: Bicarbonate buffering in acute exacerbations of chronic respiratory failure. Thorax 20:337, 1965.

60. Williams, M. H., Jr., and Levin, M.: Sudden death from bronchial asthma. Amer. Rev. Resp. Dis. 94:608, 1966.

Cases such as this continue to be reported emphasizing the extreme importance of recognizing the full nature of the asthmatic syndrome, the necessity for avoiding excessive doses of epinephrine and sedatives, and the importance of airway control and bronchial evacuation. It is worth noting that the pH was not reported. The patient was receiving isuprel 3 cc per hour by aerosol, and aminophylline 100 mgm per hour during a 30 hour period of observation. He had received in addition 1 cc of epinephrine in the first 24 hours and 140 mgm of phenothiazine in the last 13 hours. Ventilatory function was deteriorating, and it's apparent that bronchial evacuation was not effective. Death was no doubt due to acute suffocation and circulatory arrest. Postmortem examination revealed the classic findings of fatal asthma.

61. Curran, W. S., Oser, J. F., Longfield, A. N., Broderick, E. G., and Culvahouse, B. M.: Glomectomy for severe bronchial asthma: a double blind study. Amer. Rev. Resp. Dis. 93:84, 1966.

This is a double blind study of 23 asthmatic patients, ten of whom had a unilateral glomectomy. There was no significant difference either in pulmonary function or in clinical course between the operated and nonoperated patients. (There are innumerable reports of negative results and all double blind studies have yielded negative results. Numerous instances of adverse results have been reported when this operation is performed on patients with severe pulmonary emphysema especially if a bilateral procedure is performed. Both the adverse results as well as the apparent symptomatic benefit stems, in part at least, from the same

mechanism, that is, a diminution in responsiveness to hypoxia with a lessened respiratory drive; thus, the patient's awareness of his difficulty is minimized while lethal hypoventilation may be in process).

62. Palmer, K. N. V.: Sputum liquifiers. Brit. J. Dis. Chest 60: 177, 1966.

Mucoid sputum which owes most of its viscid properties to an acid sialomucopolysaccharide is much more difficult to deal with than purulent sputum for several reasons. It requires more shearing force to cause it to flow. It is thixotropic, becomes less viscid with time at a constant rate of stirring. Thus ciliary activity is very important. Either steam or heated mist of water or saline reduces sputum viscidity. In previous studies the author found no advantage to use of detergents, and the alleged value of enzymes is not confirmed; side effects are emphasized. Points out action of acetylcysteine (Mucomyst) is slow, and it requires a pH of 8 or 9 for optimum effect. Most highly viscid sputum is acid which tends to inactivate Mucomyst as does oxygen. He suggests Ascoxal as an ideal agent. (Cheap, harmless, not inhibited by pus, readily water or saline soluble and fast acting.)

63. Block, A. J., and Ball, W. C., Jr.: Acute respiratory failure: observations on the use of the Morch Piston Respirator. Ann. Int. Med. 65:957, 1966.

64. Birnbaum, M. L., Cree, E. M., Rasmussen, H., Lewis, P., and Curtis, J. K.: Effects of intermittent positive pressure breathing on emphysematous patients. Amer. J. Med. 41:552, 1966.

Short term evaluation was favorable.

65. Motley, H. L., and Yanda, R.: Experimental air pollution, emphysema and ionized air. Dis. Chest 50:343, 1966.

Air ionizers of no value.

66. Ramirez-R, J.: Bronchopulmonary lavage: new techniques and observations. Dis. Chest 50:581, 1966.

Provocative technique that deserves further evaluation.

67. Modell, J. H., Giammona, S. T., and Alvarez, L. A.: Effect of ultrasonic nebulized suspensions on pulmonary surfactant. Dis. Chest 50:627, 1966.

No adverse effect observed from nebulized water, saline or alevaire.

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These studies emphasize the role of inactivity and physical reconditioning in the disability of chronic obstructive pulmonary disease, as well as the potential for regular exercise rehabilitation programs as an adjunct to the total treatment of these patients. Small amounts of supplemental oxygen will serve to facilitate exercise in those patients not otherwise able to negotiate increased levels of physical activity.

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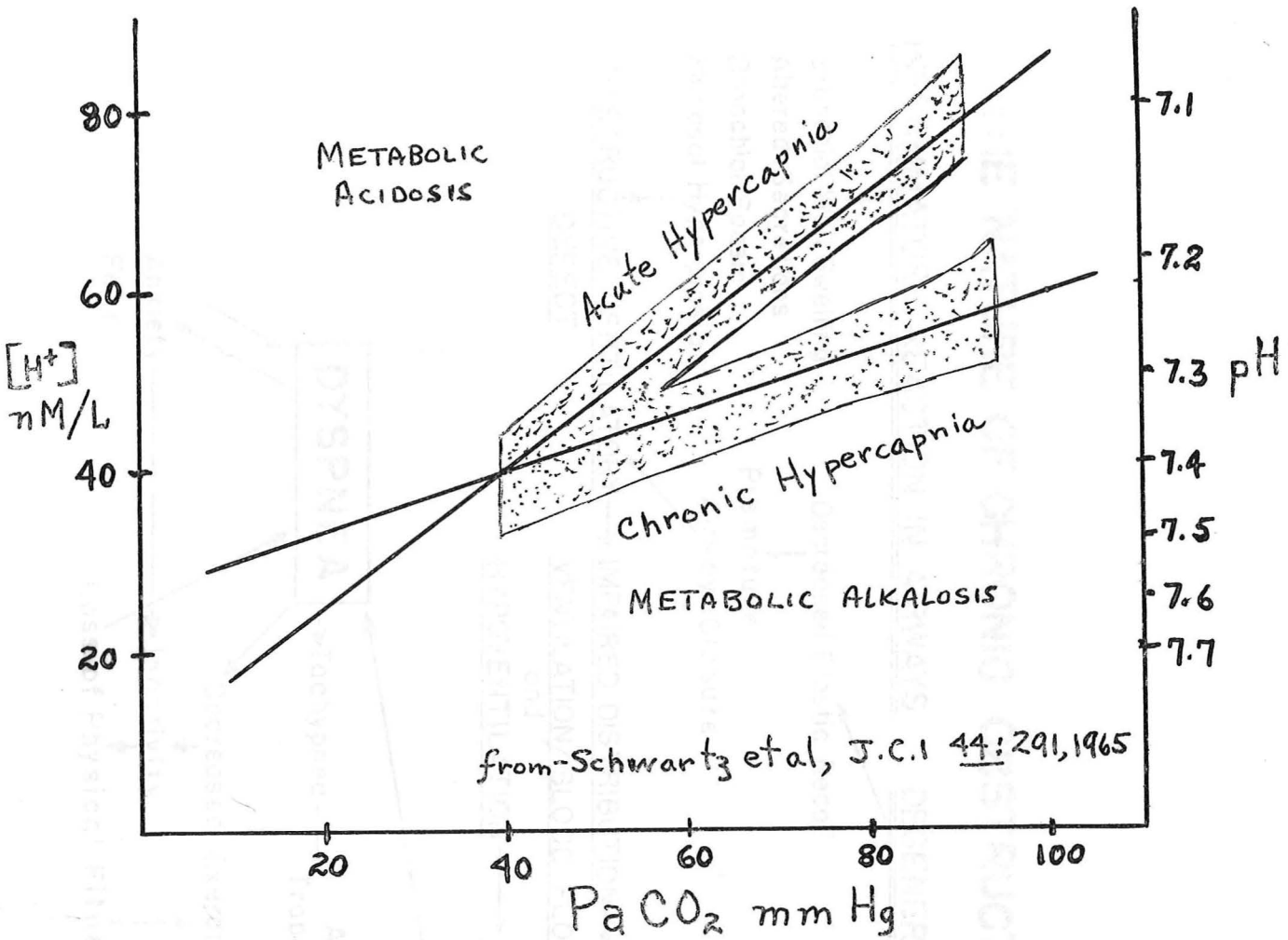

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